

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference UMD-0067		Date of mailing (day/month/year) 16 MAR 2005 FOR FURTHER ACTION See paragraph 2 below	
International application No.	International filing date (day/month/year)	Priority date (day/month/year)	
PCT/US04/24351	29 July 2004 (29.07.2004)	30 July 2003 (30.07.2003)	
International Patent Classification (IPC) or both national classification and IPC			
IPC(7): G01N 33/48 and US Cl.: 702/19			
Applicant			
UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

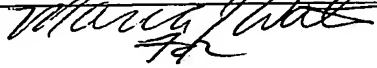
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer  Carolyn Smith Telephone No. 571-272-1600
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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing
☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>2, 4, 6, 8</u>	YES
	Claims <u>1, 3, 5, 7</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-8</u>	NO
Industrial applicability (IA)	Claims <u>1-8</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Please See Continuation Sheet

**WRITTEN OPINION OF THE
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 3-8 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims indefinite for the following reason(s):

Claims 3, 5, and 7 recite the phrase "according to" which is unclear. It is unclear what parameters and to what degree these parameters must be met to be considered "according to". Claims 4, 6, and 8 are also objected to due to their dependency from the objected claims.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1, 3, 5, and 7 lack novelty under PCT Article 33(2) as being anticipated by Hytopoulos et al. (US 2002/0169560 A1).

Hytopoulos et al. disclose a methods and a system using expression data arrays and cluster arrays wherein the expression values have been normalized, filtered, and imputed (abstract and paragraphs 0052 and 0123). The normalization of data represents normal distributions or Gaussian distributions or models. Hytopoulos et al. disclose allowing the user to select K-nearest neighbor imputation mechanism or other data imputation mechanisms (paragraph 0125). Hytopoulos et al. disclose analysis of gene expression data to form clusters (abstract). Hytopoulos et al. disclose identifying genes represented in respective rows (paragraph 0038) which represents a partitioning of rows of microarray data. Hytopoulos et al. disclose mapping rows of expression data (paragraph 0131). Hytopoulos et al. disclose using a computer readable medium in association with a computer including a processor and memory and computer instructions which are configured to cause a computer to process data (claim 15) which represents an algorithm and computer software program and product.

Claims 1-8 lack novelty and inventive step under PCT Article 33(2)-(3) as being motivated by Hytopoulos et al. (US2002/0169560 A1) in view of Cereghini et al. (US 6,496,834 B1).

Hytopoulos et al. describe a methods and a system using expression data arrays and cluster arrays wherein the expression values have been normalized, filtered, and imputed (abstract and paragraphs 0052 and 0123). The normalization of data represents normal distributions or Gaussian distributions or models. Hytopoulos et al. describe allowing the user to select K-nearest neighbor imputation mechanism or other data imputation mechanisms (paragraph 0125). Hytopoulos et al. describe analysis of gene expression data to form clusters (abstract). Hytopoulos et al. describe identifying genes represented in respective rows (paragraph 0038) which represents a partitioning of rows of microarray data. Hytopoulos et al. describe mapping rows of expression data (paragraph 0131). Hytopoulos et al. describe using a computer readable medium in association with a computer including a processor and memory and computer instructions which are configured to cause a computer to process data (claim 15) which represents an algorithm and computer software program and product. Hytopoulos et al. do not describe repeating a classification expectation-maximization algorithm until the K partitions converge.

Cereghini et al. describe a method of performing cluster analysis using Gaussian mixture parameters and implementing an Expectation-Maximization clustering algorithm iteratively (abstract). Cereghini et al. describe grouping a set of data into k clusters with k rows (partitioned) (col. 2, lines 57-63). Cereghini et al. describe the expectation-maximization algorithm converges quickly and performing iterations (col. 9, lines 34-42).

Hytopoulos et al. state that effective mechanisms for analyzing DNA array data are needed to determine which genes or combination of genes are correlated to various human conditions (paragraph 0009). Cereghini et al. state the EM algorithm is robust for noisy data and missing information (col. 7, lines 5-6). Cereghini et al. state cluster analysis does not typically work well with large databases due to memory limitations and the execution times required (col. 2, lines 32-39). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use effective means for analyzing DNA array data, as stated by Hytopoulos et al., by using algorithms supporting large databases, as stated by Cereghini et al. The person of ordinary skill in the art would have been motivated to make that modification in order to find effective ways (as stated by Hytopoulos et al. and Cereghini et al.) of correlating genes to human conditions (as stated by Hytopoulos et al.) by allowing non-statisticians to benefit from advanced

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Supplemental Box

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mathematical techniques available in a relational environment, as stated by Cereghini et al. (col. 2, lines 40-43). Thus, Hytopoulos et al., in view of Cereghini et al. motivate the instant invention.

Claims 1-8 meet the criteria set out in PCT Article 33(4), and thus meet the requirements for industrial applicability because the subject matter claimed can be made or used in industry.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on-time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.